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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,749	08/12/2002	Constance E Brinckerhoff	DC-0155	2413

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,749	BRINCKERHOFF ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed June 27, 2005. Currently, claims 6-7 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn. This action contains new grounds of rejection necessitated by amendment.

Priority

4. This application is a 371 application of PCT/US99/26610, filed November 10, 1999 and priority to provisional application 60/110,266, filed November 30, 1998.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 7 is drawn to a method for assessing the invasiveness of a tumor cell comprising detecting in the patient a AAGAT to AAGGAT polymorphism in the promoter sequence comprising SEQ ID NO: 6 wherein the presence of the polymorphism is indicative of overexpression and increased invasiveness of the tumor cell.

The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art supports the unpredictability of the broadly drawn claims.

Matsumura et al. (J. Cancer Res. Clin. Oncol., Vol. 130, pages 259-265, 2004) teaches that the frequency of 1G/2G genotypes in gastric cancer patients was similar to those in controls (p=0.57). The degree of tumor invasion, the presence of lymph node metastasis and clinical stage showed no significant association with the SNP.

Lai et al. (Gynecologic Oncology, Vol. 96, pages 314-319, 2005) teaches the MMP-1 polymorphism was assessed in high-grad squamous intraepithelial lesions (HSILs) and 197 invasive squamous cell carcinomas (SCCs). The genetic polymorphisms of the MMP-1 are not associated with the risk of HSIL and SCC. As seen in Figure 1, the survival function analysis of the MMP-1 polymorphism is not correlated to the mere presence of the 2G allele. The heterozygote G/2G showed a significantly better prognosis than the 2G/2G or G/G. It is clear that since the homozygote is note associated, that the presence of the polymorphism does not indicate survival or prognosis or invasiveness.

Ju et al. (Cancer letters, Vol. 217, pages 191-196, 2005) teaches analysis of promoter polymorphism in the matrix metalloproteinase-1 and risk of cervical cancer in Korean women. Ju teaches that Koreans with specific polymorphisms in MMP-1 are neither more susceptible to develop cervical cancer nor more vulnerable for cancer progression. The clinicopathologic parameters in cancer group also showed no significant difference suggesting the lack of an associated between the SNP and the MMP-1 promoter and invasiveness (abstract).

Babickova et al. (Studia Pneumologica et Phthiseologica, Vol. 65, No. 3, pages 116-121, 2005) teaches that the trial revealed no significant differences in the frequency of alleles and of genotypes between individual groups. Further in the metastasis free group C there was a higher proportion of 2G allele. Most probably the polymorphism 1G/2G in the promoter gene for MMP-1 is not involved in the progression of tumors.

Wenham et al. (J. of the Society for Gynecologic Investigation, Vol. 10, No. 6, pages 381-387, 2003) teaches no relationship between MMP1 genotype and histological grade, histological type, stage or tumor behavior was observed.

Benbow et al. (J. of Cell. Biochemistry. Vol. 86, pages 307-319, 2002) teaches analysis of several cell lines. The VMM5 cell line which is 1G homozygous, but invasive and expresses high levels of MMP-1 constitutively. Benbow teaches that in the absence of 2G allele and in the presence of the appropriate transcription factors, tumor cells may use alternative signal/transduction pathways and cis-acting sequences to achieve high levels of MMP-1 expression, which contribute to the ability of tumor cells to invade, *regardless* of their genotype. Despite the ability of tumor cells with the 1G genotype to produce abundant amounts of MMP-1 and to display invasive behavior, the documented association between 2G allele and enhanced cancer progression is due to the adjacent stromal cells, where this allele contributes to heightened expression of MMP1 and to tumor invasion and metastasis in vivo (page 319, col. 1).

Fang et al. (Carcinogenesis, Vol. 26, No. 2, pages 481-486, 2005) teaches that the MMP1G/5A haplotype significantly increased the risk of lymphatic metastasis compared with the 2G/6A haplotype. Fang thus suggests that the polymorphic allele is not associated with the metastasis, but rather the normal MMP1 1G allele in combination with the MMP3 5A allele.

Moreover, the specification teaches that analysis of the 1G/2G polymorphism was examined in 100 controls and several tumor cell lines. The prior art establishes that cell lines are not appropriate means for examining associations with diseases. Specifically, Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

More specifically, Sidransky et al. (US Pat. 5,856,094, January 1999) teaches a comparison between cell lines and primary tumors. In the case of p16, the rate of homozygous deletions ranged from 40-60% of breast cancer cell lines, however, neither homozygous deletions or point mutations are typically observed in primary breast carcinomas (col. 2, lines 10-15). Therefore, presence of homozygous deletions in cell lines is not indicative of primary tumors.

Moreover, Teng et al. (US Pat. 5,989,885, November 1999) teaches that discovery of mutations in cancer cell lines requires determination of whether the lesions occur in primary or metastatic tumors (col. 39, lines 49-55). Despite detection of mutation in cancer cell lines, no sequence variants were detected in 45 primary breast tumor specimens (col. 39, lines 53-56). Teng states that the MKK4r mutations in these lines were possibly generated wile these cells were cultured in vitro (col. 40, lines 5-10).

Guidance in the Specification and Working Examples

The specification teaches that MMP-1 promoter DNA may contain 1 G at position –1607 or 2 Gs at that location. The full length DNA sequence of MMP-1 with only 1 G at position –1607 is depicted in SEQ ID NO: 3. The specification provides an analysis of this 1G/2G difference in the leukocyte clone sequence and the A2058 melanoma sequence (page 8). 100 control DNAs derived from CEPH pedigrees and several tumor cell lines were analyzed. The occurrence of 2G homozygote in the CEPH controls was determined to be approximately 30%. In the tumor cell lines, it was 62.5% ($p<0.0001$)(page 8). The –1607 polymorphism is adjacent to an AP-1 site –1602 which may also influence transcription. A significant increase in transcription with the 2G promoter

construct compared with the 1G promoter construct was consistently observed in at least 4 separate donors (page 5-6).

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied before the skilled artisan could use the claimed invention as broadly as claimed.

The claims are broadly drawn to assessing the invasiveness of a tumor cell. The post-filing date art makes it clear that in numerous studies the 2G polymorphism is not associated with grade or invasiveness Thus, it is unpredictable which cancers in which populations and under which conditions are associated with the promoter polymorphism. The skilled artisan would be required to perform additional experimentation to determine under which conditions the polymorphism is associated with invasiveness prior to using the claimed method. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The analysis provided in the specification is directed at 100 controls and tumor cells lines. As discussed above, tumor cell lines are not representative of tumors from patients. Given the teachings in the specification and the art, there is no correlation that may be accurately inferred between cell lines and patients tumors.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches a lack of association between a polymorphisms and invasiveness of a tumor cell, the lack of specific guidance as to which MMP-1 polymorphism is analyzed. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 6-7 are indefinite because it is unclear whether the claims are drawn to detecting SEQ ID NO: 6 as indicative of the mutation or whether the claim is drawn to

a SEQ ID NO: 6 as the promoter sequence. The phrasing of "comprising SEQ ID NO: 6" is unclear whether the mutation comprises SEQ ID NO: 6 or whether the promoter sequence comprises SEQ ID NO: 6. It is noted from the specification that SEQ ID NO: 6 does not comprise the insertion. SEQ ID NO: 7 comprises the insertion. The claim may be written to recite "comprising detecting in the matrix metalloproteinase-1 promoter sequence a 5'-AAGAT-3' to 5'-AAGGAT-3' Ets transcription factor binding site single nucleotide polymorphism wherein the promoter comprises SEQ ID NO: 6 wherein the presence of the polymorphism is indicative of matrix metalloproteinase-1 overexpression in the cell."

B) Claim 7 is indefinite over the recitation "increased invasiveness of the tumor cell" because it is unclear what the increase is compared to. Increased is a relative term that does not have any frame of reference.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
August 17, 2005